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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/425,516	10/22/99	FREEMAN G	RPI-004C3CN

000959
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HM12/1024

EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1644	10

DATE MAILED: 10/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

UNITED STATES DEPARTMENT OF COMMERCE
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09/455516

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

EXAMINER	

ART UNIT	PAPER NUMBER
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DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 8/8/01

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 28, 63-71 is/are pending in the application.
Of the above, claim(s) 63,64,65,68,69 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 28, 66, 67, 70, 71 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendment, filed 8/8/01 (Paper No. 8), is acknowledged.
Claims 67-68 have been amended.
Claims 70-71 have been added.

Claims 28 and 63-71 are pending.

2. Applicant's election Group I, including the B7-2-specific antibody as the first agent and an agent that blocks the interaction of B7-1 with its natural ligand as the second agent in the claimed methods in Paper No. 9 is acknowledged.

Claims 28, 66, 67 and 70-71 are under consideration in the instant application.

It is noted that in the interest of compact prosecution, this Office Action will address issues under 35 USC 112, first paragraph, as they relate certain aspects of the pending claims, including non-elected species.

Claims 65, 68, 69 have been withdrawn from consideration by the examiner 37 CAR 1.142(b), as being drawn to a nonelected invention and/or species; the requirement having been traversed

There appears to be a discrepancy on the status of claims 63-64. It is noted that applicant's Remarks, filed 10/22/99 (Paper No. 2) indicate that claims 63-64 have been canceled. However, it does not appear that applicant has canceled 63-64 officially. Applicant is invited to point out when claims 63-64 have been canceled. If not, applicant is invited to cancel claims 63-64, as these claims would be subject to further Restriction.

For examination purposes, claims 63-64 will be considered withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. The substitute specification in compliance with applicant's statements, filed 8/8/01 (Paper No. 9), has been entered and is in compliance with 37 CFR 1.125(b).

According to applicant's statements, the substitute specification incorporates all of the amendments to the specification, corrects all defects (e.g. trademarks) and is free of new matter.

4. The filing date of the instant claims is deemed to be the filing date of the priority application USSN 08/280,757, filed 7/26/94, now U.S. Patent No. 6,130,316, as the previous priority applications do not appear to provide sufficient written description for the claimed "methods of inhibiting an interaction of a B lymphocyte antigen B7-2 with its natural ligand on the surface of an immune cell" an "agent which inhibits B7-2 binding with its natural ligand", "antibody reactive with CD28", "antibody reactive with CTLA4", "antibody reactive with a cytokine", a "CTLA4Ig fusion protein", a "CD28Ig fusion protein" and an "immunosuppressive drug"

While USSN 08/101,624 discloses monoclonal or chimeric antibodies reacted with the described B7 molecules for immunotherapy as well as monomeric B7 molecules for downregulating or preventing B lymphocyte antigen functions; USSN 08/101,624 does not disclose the "limitations" indicated above.

If applicants disagree, applicants should present a detailed analysis as to why the claimed subject matter has clear support in the parent application. Applicant is invited to verify the priority date of the instant claims, including written support and enablement under 35 USC 112, first paragraph.

5. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant should amend the first line of the specification to update the status of the priority documents.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

7. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

8. Formal drawings and photographs have been submitted which fail to comply with 37 CAR 1.84. Please see the enclosed form PTO-948.

9. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

10. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 28, 66, 67 and 70-71 (as well as 65, 68) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of T:B interaction s with certain antagonists of CD28:B7 interactions under certain conditions would be effective in inhibiting their interaction of a B lymphocyte antigen B7-2 with its natural ligand on the surface of an immune cell, particularly in vivo or in therapeutic methods to treat pathological conditions such as autoimmunity including diabetes, myasthenia gravis, arthritis and SLE transplantation, infectious diseases and neoplasia (see page , paragraph of the instant specification)

There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed methods to inhibit functional CD28-B7 interactions to regulate B lymphocyte-mediated interactions and immune responses in vivo by administering by any "agent", including "anti-B7-2 antibodies", commensurate in scope with the therapeutic methods encompassed by the claimed invention.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol., 1992; see entire document, particularly page 558, column 2).

Blazar et al. (J. Immunol. 167: 3250-3259, 1996) discloses that issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10.

Blazar et al. (J. Immunol. 167: 3250-3259, 1996) discloses that anti-CD80 or anti-CD86 antibodies were ineffective in preventing T cell CD8-mediated GVHD lethality; that each antibodies was partially effective in CD4-mediated GVHD lethality and that the combination of anti-CD80 and anti-CD86 antibodies were effective in preventing GVHD lethality in murine experimental models (see entire document, including the Abstract)

Similarly, Perrin et al. (J. Neuroimmunol 65: 31-39, 1996) discloses that in contrast to the effective treatment of disease with CTLA-4 Ig; anti-CD80 (B7-1) attenuated the first clinical disease episode but not the relapse, anti-CD86 (B7-2) had no significant effect on the course of disease, and the combined treatment with anti-CD80 plus anti-CD86 resulted in the exacerbation of disease (see entire document). It is also noted that CTLA-4 Ig had a marked but incomplete therapeutic effect in the EAE model.

In addition, Yi-qun et al. (Intl. Immunol. 8: 37-54, 1996) discloses that their findings have a number of important implications for therapeutic approaches (see entire document, particularly Discussion, last paragraph). It is clear that inhibition of T cell response to soluble antigens will require the blocking of both B7-2 and B7-1 to be effective. More, important it is unlikely that ongoing T cell response will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases.

Therefore, it is acknowledged that the administration of the CD28:B7 inhibitor CTLA-4 Ig can result in immunosuppression as observed in several model systems. However even in these systems; the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention.

The instant Examples disclosed in the present specification are consistent with the observations that CTLA-4Ig is a more potent inhibitor than B7-specific antibodies.

The instant specification discloses that B7-2Ig is a potent stimulator of activated T cells for the production of cytokines.

Sturmhoefel et al. (Cancer Research 59: 4964-4972, 1999) disclose that B7-2 fusion proteins promote antitumor responses (see entire document, including the Abstract and Discussion).

Therefore, it does not appear that the claimed or scope of soluble form of B7-2 would inhibit the interaction of B7-2 in a manner consistent with the instant disclosure.

It is noted that the instant specification discloses the use of a soluble monomeric form of B7-2 as an inhibitor.

Applicant is invited to provide objective evidence to indicate that monomeric B7-2 inhibits immune responses both in vitro and in vivo.

In contrast to the role and avidity that the CD28:B7 inhibitor CTLA-4 Ig appears to have in vivo, there is insufficient objective evidence in the instant application that either the claimed B7 or B7 fusion proteins alone can inhibit T cell function or interactions in vivo and the objective evidence above would indicate that neither would be predicted to inhibit in vivo function or interactions.

While CTLA-4Ig appears to be immunosuppressive in certain systems, it is not clear that it inhibits the targeted conditions encompassed by the claimed methods.

Similarly, it is not clear that there is objective evidence that supports that ability of CD28Ig, "any agent that blocks the interaction of B7-1 with its natural ligand" and/or "antibody that binds a cytokine" would be immunosuppressive in the targeted conditions encompassed by the claimed methods.

For example, Debets et al. (Immunol. Today 15: 455-458, 1994) discloses that potential therapeutic uses of cytokine antagonists, such as antibodies, including the importance of testing appropriate models and the limitations of double-edged sword of such antagonists (see entire document, including page 457, column 3).

Also, the specification as filed does not appear to identify the appropriate cytokine targets and the appropriate conditions to be targeted by said anti-cytokine antibodies in combination with the B7-2-specific antagonists.

Immunosuppression is much easier to achieve under controlled in vitro conditions that experienced in the human immunoregulatory diseases such as transplant rejection autoimmune diseases, allergies and viral infections encompassed by the claimed invention (see Therapeutic Uses by Downregulation of Immune Responses). Further, in animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Therefore, it should be noted that although the animal models validate concepts based on studies of human disease, such studies are limited to the acute as opposed to chronic nature of the disease. Immunosuppression is much easier to achieve under such controlled conditions to defined antigens in mice than that experienced in the human immunoregulatory diseases targeted or encompassed by the claimed invention.

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering anti-B7-2 antibodies (on monomeric B7-2) alone. The specification does not teach how to extrapolate data obtained from the disclosed in vitro assays of blocking B7-2 binding to CTLA4 and CD28 or from other CD28:B7 inhibitors such as CTLA4-Ig to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention. Therefore, there is insufficient objective evidence that accurately reflects the relative efficacy of the claimed method or therapeutic strategies to regulate CD28-B7 interactions in vivo as a therapeutic method by administering anti-B7-2 antibodies (or monomeric B7-2) in the absence of other inhibitors, commensurate in scope and encompassed by the claimed methods.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective costimulatory-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting an interaction of a B lymphocyte B7-2 antigen in the targeted therapeutic methods encompassed by the claimed invention.

12. This is a rejection under 35 USC § 112, first paragraph, "written description" (and not new matter).

Claims 28, 66, 67 and 70-71 (as well as 65, 68) are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

There is insufficient written description encompassing "B7-2" and a "natural ligand" for B7-2" because the relevant identifying characteristics such as structure of other physical and/or chemical characteristics of both the "B7-2" and the "natural ligand", are not set forth in the specification as filed, commensurate in scope with the claimed invention.

In addition, there is insufficient written description encompassing the antibody that is reactive with a cytokine" "CD28", "CTLA4" and "cytokine" as well as "an agent that blocks the interaction of B7-1 with its natural ligand" encompassed by the claimed methods.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The instant specification discloses human (SEQ ID NO: 2) and murine/mouse (SEQ ID NO: 23) B7-2 molecules and CTLA-4 and CD28 as the natural ligands of said human/murine/mouse B7-2 molecules.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses targeting any B7-2 : natural ligand interaction, yet the instant specification does not provide sufficient written description as to the structural features of said B7-2 molecule : natural ligands and the correlation between the chemical structure and the function of the genus of B7-2 : natural ligands. The reliance on the disclosed limited examples of the B7-2 molecule and natural ligands in the specification as filed does not support the written description of any B7-2 molecule and natural ligand thereof. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities. Therefore, structurally unrelated B7-2 molecules and natural ligands thereto encompassed by the claimed invention other than B7-2 set forth in SEQ ID NOS: 2 and 23 as well as CTLA-4 and CD28 would be expected to have greater differences in their structures, expression and activities.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying a B7-2 molecule and/or a natural ligand thereto, encompassed by the claimed invention. There is insufficient guidance based on the reliance of B7-2 set forth in SEQ ID NO: 2 and 23 to direct a person of skill in the art to select or to predict particular sequences as essential for identifying B7-2 molecules encompassed by the claimed specificities.

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

The specification does not disclose nor identify B7-2 nor natural ligands thereto other SEQ ID NOS: 2 and 23 and CTLA-4/CD28 of human murine/mouse origin.

B7-2 and natural ligands thereto molecules differ in structure and physicochemical properties. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

For the same or nearly the same reasons indicated above, applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "an antibody that is reactive with a cytokine" "CD28", "CTLA4" and "cytokine" as well as "an agent that blocks the interaction of B7-1 with its natural ligand" encompassed by the claimed methods

The specification does not appear to identify "cytokine" antibody specificities, nor provide for the written description of CD28" or "CTLA4 of any mammalian species as well as any "agent that blocks the interaction of B7-1 with its natural ligand" encompassed by the claimed methods.

Again, it has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological and pharmacological activities. For example, it is noted that "cytokines" is a broad diverse class of molecules, which do not share critical common structural attributes.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying any "CD28", "CTLA-4", "cytokine" specificity or "agent", encompassed by the claimed invention. There is insufficient guidance based on the reliance of a limited disclosure to direct a person of skill in the art to select or to predict particular sequences as essential for identifying any "CD28", "CTLA-4", "cytokine" specificity or "agent", encompassed by the claimed invention. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of ligands of any "CD28", "CTLA-4", "cytokine" specificity or "agent", or because the genuses are highly variable,

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of "B7-2", "natural ligand" thereto, "CD28", "CTLA-4", "cytokine" specificity or "agent; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

13. Claims 28, 66, 67 and 70-71 (as well as 65, 68) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the human and murine/mouse B7-2, CD28, CTLA-4 (B7-1 specificity) as disclosed in the specification as filed, does not reasonably provide enablement for any B7-2, CD28, CTLA-4, ligand or agent".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the B7-2, CD28, CTLA-4, ligands , agents other than those encompassed by the disclosure of the particular human/murine/mouse costimulatory molecules disclosed in the specification as filed. B7-2, CD28, CTLA-4, ligand or agent may have some notion of the activity of the receptor, ligand or agent, claiming biochemical molecules by a particular name given to the protein (e.g receptor or ligand) by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any B7-2, CD28, CTLA-4, agent or natural ligand.

For example, Coyle et al. (Nature Immunology 2: 203-209, 2001) disclose that B7-1 and B7-2 exhibit pronounced differences in structural and functional characteristics (page 204, column 1; The B7-1 and B7-2 Family) and disclose the increasing complexity in costimulatory signal regulating T cell function, wherein a number of molecules are poorly understood and likely have distinct roles in regulation T cells (see entire document).

Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology 10: 383-389, 1992; see entire document, particularly page 386, column 3, paragraph 4).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. The instant invention encompasses any B7-21, CD28, CTLA-4, agent that blocks the interaction of B7-1 specificity yet the instant specification does not provide sufficient guidance and direction as to the structural features of said diverse molecules and the correlation between the chemical structure and the desired molecules or specificities. The reliance on the disclosed limited examples set forth in the specification does not support the enablement for any costimulatory molecules, agents or ligand encompassed by the claimed invention.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands. Therefore, structurally unrelated costimulatory molecules, agents and ligands encompassed by the claimed invention other than the particular human or murine/mouse costimulatory molecules set forth in the specification would be expected to have greater differences in their activities. For example, it is noted that antibodies and soluble receptors do not share critical common structural attributes, as antibodies and soluble proteins differ in structure and physicochemical properties.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to costimulatory molecules, ligands and agents with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the certain costimulatory molecules, ligands and agents disclosed as filed does not appear to provide sufficient enabling support for any costimulatory molecule, ligand or agent encompassed by the claimed invention and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using ligands and CD28 receptors would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

14. Claims 28, 66, 67 and 70-71 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28, 66, 67 and 70-71 are definite in its recitation of "inhbiting the interaction .... with its natural ligand" because the nature of the "interaction" and the "ligand" is ambiguous. Therefore, the metes and bounds of the claimed methods encompassing inhibiting interactions and ligands are not readily apparent..

The claims are indefinite in the recitation of "ligand" in that they only describe the products of interest by an arbitrary protein name. While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the ligand. Applicant should particularly point out and distinctly claim the "ligand" by claiming sufficient characteristics associated with the "ligand" (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

16. As pointed out above, applicant is invited to indicate the priority date of the instant claims. In the absence of a clear priority date, the following art rejections are set forth.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 28, 66, 67 and 70-71 are rejected under 35 U.S.C. § 102(e) as being anticipated by de Boer et al. (U.S. Patent No. 5,747,034) (see entire document).

De Boer et al. teach methods of inhibiting immune responses both in vitro and in vivo with combinations of B7-specific inhibitors, including the use of both B7-1-specific and B7-2-specific antibodies (see entire document, including Columns 14-16, Compositions Including Immunosuppressive Agents and Formulations and Methods of Administration). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods of inhibiting immune responses with B7-specific antibodies.

19. Claims 28, 66, 67 and 70-71??? are rejected under 35 U.S.C. § 103(a) as being unpatentable over de Boer et al. (U.S. Patent No. 5,747,034) in view of Linsley et al. (U.S. Patent No. 6,090,914.

De Boer et al. teach methods of inhibiting immune responses both in vitro and in vivo with combinations of B7-specific inhibitors, including the use of both B7-1-specific and B7-2-specific antibodies (see entire document, including Columns 14-16, Compositions Including Immunosuppressive Agents and Formulations and Methods of Administration).

In addition to the teachings of De Boer et al.; Linsley et al. teach that the potent immunosuppressive

CTLA4 reagent binds both B7-1 and B7-2, both of which are important for T cell activation events (e.g. see column 3, paragraph 2; column 4, Summary of the Invention) as well as anti-B7 antibodies can be used to inhibit the interactions of CD28-positive or CTLA4-positive T cells with B7-positive cells (columns 16-17, overlapping paragraph). Column 28, paragraph 3 and column 38, paragraph 3 indicated that the effectiveness of CTLA4Ig is due to it affinity for B7, including B7-1 and B7-2. Linsley et al. teach the art known use of combination therapy (Column 17, paragraph 2) as well as treating various conditions by inhibiting CTLA-4:B7 interactions (see Use on columns 14-18, including column 17, paragraph 3).

Given the teachings of DeBoer et al. and Linsley et al.; the ordinary artisan would have been motivated to target both B7-1 and B7-2 with B7-specific antibodies in order to achieve a higher efficacy in inhibiting immune responses in vitro and in vivo, given the contribution of both to B:T cell interactions as well as observations and/or indications that CTLA4Ig achieve its efficacy by inhibiting both B7-1 and B7-2. One of the ordinary skill in the art would have been motivated to target both in vitro and in vivo immune assays with B7-1- and B7-2-specific antibodies to determine the role of these molecules in immune interactions as well as to test these reagents in order to treat various diseases or disorders associated with the immune response. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. No claim allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
October 18, 2001

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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